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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Patricia A. Kammerer
Howrey Simon Arnold & White, LLP
750 Bering Drive
Houston, TX 77057-2198

EXAMINER
DIBRINO, MARIANNE NMN

ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 10/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.	Applicant(s)
09/747,029	Union et al.
Examiner	**Art Unit**
Marianne DiBrino	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *4/2/01 and 7/8/02*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22* is/are pending in the applica

4a) Of the above, claim(s) *10, 11, 16, and 17* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9, 12-15, and 18-22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7 Filed 4/2/01 & 8/22/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment filed 4/2/01 (Paper No. 6) and Applicant's response filed 7/8/02 (Paper No. 17) are acknowledged and have been entered.

2. Applicant's election with traverse of Group X (claims 1-9, 12-15 and 18-22) , drawn to a cyclic peptide comprising the primary amino acid structure consisting of SEQ ID NO: 4, a composition thereof, and immunotoxin comprising said peptide and composition thereof, and kit comprising said peptide, and species of SEQ ID NO: 12 in Paper No.17 is acknowledged.

The traversal is on the grounds that the examination of all, or at a minimum more than one of the groups I-XII does not impose a serious burden on the Examiner, i.e., that there are sufficiently few members of the Markush group which can be examined without serious burden, that the said members possess two common structural features, namely the presence of at least one citrulline residues and the presence of 2 cysteine residues separated by less than 12 amino acid residues, that are responsible for the three dimensional structure of the peptides and that the examination of cyclic peptides can be accomplished in the same application as linear peptides.

Applicant's arguments have been considered, but are not deemed persuasive for the following reasons. Although the claimed peptides have a peptide turn comprising at least one citrulline residue and two cysteine residues separated by less than 12 amino acid residues, the claimed peptides have different lengths, primary amino acid structures and the citrulline residue(s) and the cysteine residues are present at different positions in the different peptides, necessitating different searches. For example, the peptide of the elected Group X has citrulline at position 12 and may have it at position 11 additionally, cysteine at positions 9 and 14 and the peptide is 18 amino acid residues in length, whereas the peptide of non-elected Group III has citrulline at position 7 and may have it at position 8 additionally, cysteine at positions 5 and 12 and the peptide is 14 amino acid residues in length. Further, the amino acid residues at other positions are different. In addition, Applicant's admission in the specification on page 17 at the last paragraph and continuing on to page 18, is that the length of the peptides as well as the nature of the side chain interactions between amino acid residues other than the cysteine and citrulline residues are important with regard to the three dimensional structure of the peptides. With regard to Applicant's argument about cyclic and linear peptides, this is not found persuasive because the cyclic peptides, in contrast to the linear peptides, are additionally classified in class 514, subclasses 9 and 11. This constitutes divergent searches.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 10, 11, 16 and 17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Upon consideration of a search of the prior art, since SEQ ID NO: 4 and 12 appear to be free of the prior art, the search has been extended to include the peptides taught by the prior art references cited below in this action.

Claims 1- 9, 12-15 and 18-22 are currently being examined.

3. It is noted that this application appears to claim priority to EP 99870280.7 and EP 00870195.5. It is suggested that Applicant move the foreign priority claim to page 2, line 1 of the specification before the section entitled "Field of the Invention" rather than before "Background of the Invention".

4. The reference "B4"crossed out in the Form 1449 filed 4/2/01 has not been considered because no translation has been provided.

5. The disclosure is objected to because of the following informality:

The specification on page 6 at the Brief Description of the Figures at line 24 does not disclose "A-D" after "Figure 3." In addition, it is suggested that Applicant capitalize "a", "b", "c", "d" that appear at the end of the sentence on lines 24 and 25.

Appropriate correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9, 12-15 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how to use the claimed peptide comprising SEQ ID NO: 4 or SEQ ID NO: 12, composition thereof and immunotoxin or kits comprising the said peptide for diagnosis or treatment of autoimmune diseases including rheumatoid arthritis. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass peptides that are not specifically recognized by autoimmune antibodies from patients suffering from rheumatoid arthritis (RA) or other autoimmune diseases.

The specification discloses (on page 2 at line 24-31 and continuing on to page 3 at lines 1-3) that serological support for diagnosing RA is not very well established and is based mainly on the presence of rheumatoid factors (RF), that a number of RA patients are RF negative while RF is also found in a variety of other rheumatic diseases. The specification further discloses (on page 13 at lines 12-30 and page 14 at line 31) that a set of citrullinated peptides generated using molecular modelling and computational chemistry which are reactive with the autoimmune antibodies have a similar three-dimensional structure comprising a peptide turn. The specification discloses testing a number of previously diagnosed (on the basis of ACR criteria) RA patients' sera for reactivity with multiple citrullinated peptides of the invention (on page 35-41). The specification discloses a high specificity for reactivity of the peptides with the RA sera and complementarity with the RF test. The specification does not disclose treating rheumatoid arthritis or any other autoimmune disease in a subject animal, nor diagnosing patients with rheumatoid arthritis or any other autoimmune disease.

Evidentiary reference Jaarsveld et al (Clin Exp Rheum 1999, 17: 689-697, IDS reference) teaches that the CCP-ELISA (CCP, a cyclic citrullinated peptide) detects antibodies which recognize a subset of antiperinuclear factor and AKA (APF, profilaggrin, a potential prognostic marker for RA) determinants and that the reactivity of RA sera to different citrullinated peptide variants is highly diverse (especially page 695 at columns 1 and 2). Jaarsveld et al further teach that testing for APF by indirect immunofluorescence and the CCP-peptide ELISA assay together may have prognostic value to predict mild rheumatoid arthritis disease, but that reliable identification at baseline of individual patients with progressive disease is still not possible (especially Abstract). Jaarsveld et al also teaches that rheumatoid arthritis patients are a heterogeneous population (especially page 695 and 696); for example with respect to radiological damage scores the combination of RF and APF is a better prognostic marker than the single tests alone (especially page 696 at column 1, first paragraph). Evidentiary reference Schellekens et al (Arthritis & Rheum, 2000, 43(1): 155-163, IDS reference) teaches that although the anti-CCP ELISA assay is highly specific for rheumatoid arthritis, that further studies are clearly needed to substantiate the prognostic values of the anti-CCP assay, and that combining the anti-CCP assay with the IgM-RF ELISA increased the positive predictive value (especially page 162 at the last column).

Accordingly, there is a high level of unpredictability in diagnosing and treating subjects with autoimmune diseases including rheumatoid arthritis using the claimed citrullinated peptides and Applicant does not provide direction or guidance to do so. There is insufficient guidance in the specification as to how use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 8 and 12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite in the recitation of "small volume" in line 2 because it is not clear what the metes and bounds of the said limitation are. keep

Regarding claim 12, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

10. Claims 13-15 and 19-20 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can not depend from any other multiple dependent claim. See MPEP § 608.01(n).

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 2, 4, 5, 8, 12, 15, 19, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by WO98/43660 (IDS reference"B2"filed 4/2/01) as evidenced by US 5,994,379.

WO98/43660 teaches a synthetic cyclic peptide comprising a sequence of less than 50 amino acid residues containing at least one citrulline residue between 2 cysteine residues spaced 4 amino acid residues apart, with the amino acid residues flanking the said citrulline residue having small volume, and pharmaceutical composition thereof for nasal or oral administration (especially page 9 at lines 1-29, page 13 at lines 8-27, claims 1-2, 10-12). WO98/43660 further teaches that the said peptide can be used to treat irritable bowel syndrome (especially page 8 at lines 4-5).

Evidentiary reference US 5,994,379 discloses that irritable bowel syndrome is an autoimmune disease (especially column 9 at lines 20-26).

While WO98/43660 does not teach the said peptide is specifically recognized by autoimmune antibodies from patients suffering from rheumatoid arthritis, the claimed peptide appears to be the same or similar to the peptide of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the peptide of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Note that the claims are drawn to compositions comprised of a peptide and that claimed recitation of intended use in kits does not carry any patentable weight per se. While the claim recites a kit, no positive recitation of the ingredients distinguishes it over the references; therefore the kit is encompassed by the references. Also note that the claimed recitation of intended use in instant claims 12, 15, 20 and 22 does not carry any patentable weight per se. A compound is the same compound irrespective of its intended use.

The reference teachings anticipate the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-6, 8, 12-15 and 18-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/28344 (6/10/99, IDS reference "B3" filed 4/2/01) in view of Jaarsveld et al (Clin. Exp. Rheum. Vol. 17, 1999, pages 689-697, IDS reference "C4" filed 4/2/01) and admissions in the specification on page 8 at lines 18-20.

WO 99/28344 teaches circularized synthetic peptides (i.e., cyclic) containing less than 50 amino acid residues and containing at least one citrulline residue and which react with antibodies from patients with rheumatoid arthritis (RA). WO 99/28344 further teaches pharmaceutical compositions comprising the peptides for therapy or diagnosis, i.e., medicaments for treatment or a diagnosticum for rheumatoid arthritis or other autoimmune diseases, diagnostic kits, including wherein the peptides are attached to specific locations on

solid substrate and combined with other peptide epitopes that can characterize autoimmune diseases or that are in solution for use as competitors, and immunotoxin molecules comprising the peptides, medicaments in which the peptide are in tandem repeats or branched forms to increase the size of the antigen-immune complexes to increase clearance and decrease immune complex deposition in the body, and the peptides in biotinylated form (entire document, especially abstract, pages 4-7, page 8 at lines 10-30 and continuing on to page 9 at lines 1-2 and 9-15, 23-31, page 10 t lines 1-8 and 21-31, page 11 at lines 1-31, Table 1 on page 13 and lines 25-31, page 20 at lines 1-25, page 23, page 26, claims). WO 9928344 teaches an overview of the amino acid substitutions that could form the basis of analogs of the peptides such as Cys for Ser, Thr or Met (especially Table 1 on page 13). WO 99/28344 teaches that the advantage of circularized forms of the said peptides was well known in the art and relates to an increased affinity of a conformationally constrained peptide as compared with the more randomly coiled forms of linear peptides (especially page 11 at lines 7-10).

WO 99/28344 does not teach that at least one citrulline residue is present in between two cysteine residues and that there are less than 12 amino acid residues between cysteine residues.

Jaarsveld et al teach an citullinated cyclic peptide that was cyclized by substituting serine residues by cysterine (especially page 691, column 2 at the first full paragraph).

Applicant's admission on page 8 at lines 19-20 is that a linear peptide can be circularized by any known method in the art, for example by the formation of a disulfide bond between two cysteine residues.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted cysteine for serine in a peptide taught by WO 9928344 such as the peptides in claim 3 as taught by WO 99/28344 and to produce a cyclic peptide as taught by Jaarsveld et al and WO 99/28344.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to cyclize the peptide as taught by Jaarsveld and as per applicant's said admission in the specification, and because WO 9928344 teaches the advantage of cyclizing the peptides for conformational stability.

15. SEQ ID NO: 4 and 12 appear to be free of the prior art.

16. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
September 23, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600